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METHOD AND COMPOSITION FOR THE
TREATMENT OF DIABETES

TECHNICAL FIELD OF THE INVENTION

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This invention is directed to a novel method and composition for the treatment of diabetes mellitus (Type I, Impaired Glucose Tolerance ["IGT"] and Type II). More specifically, this invention pertains to a novel method of
10 and compositions for orally treating diabetes mellitus by administering to a person afflicted with diabetes mellitus one or more sensitizer chemicals, which increase the cells ability to utilize glucose, along with orally ingested medications for the treatment of diabetes mellitus.

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BACKGROUND OF THE INVENTION

It is estimated that 1.5 to 2% of the entire population of the world suffers from diabetes mellitus of
20 some type. Diabetes mellitus is a chemical disorder of the human body primarily involving an inability of the body to properly utilize sugar and other chemical compounds in the metabolism of the body. It is characterized by an elevation in the concentration of sugar in the blood and
25 also by the appearance of sugar in the urine.

In general terms, diabetes mellitus is classified into three types, namely, Type I, IGT and Type II. In Type I diabetes, the beta cells in the pancreas, probably
30 through an auto-immune reaction, cease producing insulin into the bloodstream of the person. Insulin is a chemical substance which is normally secreted into the bloodstream by beta cells within the pancreas. Insulin is vitally important to the person because it enables the person to
35 properly utilize and consume sugar in the bloodstream as part of the metabolism process.

In Type I cases, where the pancreas has ceased producing insulin, it is necessary for the afflicted person

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to inject insulin directly into the bloodstream at prescribed periodic intervals and dosages in order to control the level of sugar in the blood. This is called intravenous injection. Oral ingestion of insulin is also possible but usually less effective due to the degradation of insulin caused by the passage through the stomach and upper intestine.

In IGT and Type II diabetes, the pancreas continues to produce insulin but, some or all of the insulin may fail to bind to the body's cell receptors and/or internalization of insulin in the cells is reduced. In such cases, there may be a sufficient level of insulin in the blood, but the ability of the cells to uptake glucose is reduced or non-existent because of reduced internalized insulin.

The existence of Type I, IGT or Type II diabetes in a person is usually determined by an oral glucose tolerance test (OGTT). OGTT is a test in which the fasting patient is given a known amount of glucose (sugar) by mouth, and the blood is tested at intervals thereafter to note the quantity of sugar in the blood. A curve is then constructed from which important information about the person can be drawn. The glucose tolerance test curve will typically show whether the patient is hyperglycaemic (diabetic) or whether the patient has too little sugar in his or her blood and is therefore hypoglycaemic.

Symptoms of hyperglycaemia can be headaches, increased urination, thirst, nausea, weight loss, fatigue and coma. Hyperglycaemia can be caused by Hypoinsulinism, a condition in which the insulin producing beta cells of the pancreas fail to manufacture insulin or manufacture and secrete a reduced amount of insulin into the bloodstream. In such cases, levels of sugar in the blood are dramatically increased.

Hyperglycaemia can also be caused by failure of some or all of the available insulin in the blood to bind to the body's cell receptors and/or internalization of insulin in the cells is reduced.

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Hypoglycaemia (too little sugar) is also a blood condition that diabetics must constantly guard against. The symptoms of hypoglycaemia are abrupt episodes of intense hunger, trembling of the hands and body, faintness, black spots before the eyes, mental confusion, sweating, abnormal behaviour, and, in severe cases, convulsions with loss of consciousness. In such cases, examination of the blood at the time of these attacks will show an extremely low level of circulating sugar in the blood.

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Hypoglycaemia can be caused by Hyperinsulinism, a condition in which the insulin producing beta cells of the pancreas manufacture and secrete an excessive amount of insulin into the bloodstream. Levels of sugar in the blood are therefore dramatically reduced.

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Transfer of glucose from the blood stream to the body cells is believed to be enabled by the binding of insulin to the cell receptors. Receptor bound insulin then increases the amount of insulin that is internalized in the cell. Internalized insulin results in increased utilization of glucose in the cell and consequently increased metabolism. A drug that sensitizes the surface of a body cell to increase the cell's internalization of insulin or is believed or purported to function by sensitizing a cell to insulin is known herein as an "insulin sensitizer".

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The following is a list of drugs that are being or have been tested as insulin sensitizers:

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1. BRL-49653 as produced by SmithKline Beecham or by some other advocate.

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2. *Pioglitazone HCL* as produced by Takeda or some other advocate.
- 5 3. *Troglitazone, Noscal or Resiline* as produced by Sankyo, Glaxo Wellcome or Warner-Lambert.
4. MC 555 as produced by Mitsubishi or some other advocate.
- 10 5. ALRT 268 as produced by Ligand or some other advocate.
6. LGD 1069 as produced by Ligand or some other advocate.
- 15 7. Chromic Picolinate.
8. Diab IITM (otherwise known as V-411) or Glucanin and produced by Biotech Holdings Ltd. or Volque
20 Pharmaceutical.

as a Intravenous injection is the anathema of all Type I and II diabetics forced to inject insulin. These diabetics today are cursed to a lifelong ritual of having
25 to inject insulin into their bloodstream, usually several times a day, in order to keep the level of insulin in the blood within prescribed levels.

Considerable research is being conducted to
30 develop an insulin which can be orally ingested for the treatment of Type I or II diabetes. Such an orally ingestible insulin would be welcomed by Type I and Type II diabetics because it would no longer be necessary for them to undergo a daily routine of intravenous insulin
35 injections. Unfortunately, to date, an orally ingested insulin has not yet been successfully developed.

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A major problem is that stomach acids and gut enzymes of the person destroy most of the orally ingested insulin and hence the amount of ingested insulin that reaches the bloodstream is less than what is therapeutically required for the diabetic to function normally. Time release systems, which protect the insulin while it passes through the stomach and upper intestine, and release the insulin subsequently, are being researched to alleviate this problem. The theory of these time release systems is to incorporate the insulin with appropriate time release mechanisms so the insulin is not released until after the time release-insulin combination has passed through the stomach and the preliminary stages of the digestive process.

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IGT and Type II Diabetes can be treated with one or more classes of drugs generally known as hypoglycaemics to reduce blood glucose levels.

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One class of hypoglycaemics are known as "sulfonylureas". Trade-marks for commercially available sulfonylureas include Glucotrol, Diabinese, DiaBeta, Micronase, Tolinase and Orinase. Sulfonylureas appear to stimulate the pancreas and increase the production of insulin from the beta cells in the pancreas. Unfortunately, there are potential unfavourable side effects from the use of sulfonylureas. Therefore, the less a patient is required to use a sulfonylurea, the fewer side effects are likely to be experienced by that patient.

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Another class of hypoglycaemics are known as "biguanides". Trade-marks for some commercially available biguanides include Metformin and Glucophage. The physiological action of biguanides is not completely understood. However, biguanides may divert glucose before reaching the blood stream thereby reducing blood glucose levels. Biguanides may also increase cell receptor

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sensitivity. There are potential unfavourable side effects from the use of biguanides by a patient so the less a patient uses a biguanide, the less likely the patient is to experience unfavourable side effects.

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A further class of hypoglycaemics is known as the "alpha-glucosidase inhibitors". Trade-marks for some alpha-glucosidase inhibitors include Precose, Prandase, and Acrabose. These drugs are believed to bind glucose in the gastrointestinal tract thereby reducing glucose absorption. Because there are unfavourable side effects associated with the use of alpha-glucosidase inhibitors, the less a patient uses such drugs, the less the patient is likely to experience unfavourable side effects.

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The following U.S. patents are relevant to the art of orally administered insulin:

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| 20 | 4,362,719 - | Therapeutic Method and Compositions for the Treatment of Juvenile Diabetes Mellitus |
| | 4,579,730 - | Pharmaceutical Compositions Containing Insulin |
| 25 | 4,602,043 - | Treatment for Hypoglycemia |
| | 4,696,815 - | Anti-Diabetic Pharmaceutical Forms and the Preparation Thereof |
| 30 | 4,708,868 - | Anti-Diabetic Pharmaceutical Forms and the Preparation Thereof |
| | 4,826,684 - | Composition for, and Method of, Treatment of Diabetes |
| 35 | 4,849,405 - | Oral Insulin and a Method of Making the Same |
| | 4,871,739 - | Substituted 6H-7,8-dihydrothiapyrano (3,2-D)-pyrimidines as Hypoglycemic Agents |
| 40 | | |
| | 4,873,080 - | Oral Anti-Diabetic Pharmaceutical Compositions and the Preparation Thereof |
| 45 | | |

	4,963,526 -	Oral Insulin and a Method of Making the Same
5	4,978,667 -	Substituted 6H-7,8-dihydrothiapyrano (3,2-d)-pyrimidines as Hypoglycemic Agents
10	5,057,517 -	Piperazinyl Derivatives of Purines and Isosteres Thereof as Hypoglycemic Agents
	5,187,154 -	Diagnosis and Treatment of Humans with Diabetes or at Risk to Develop Diabetes
15	5,206,219 -	Oral Compositions of Proteinaceous Medicaments
	5,234,906 -	Hyperglycemic Compositions
20	5,284,845 -	Use of Oral Diazoxide for the Treatment of Disorders in Glucose Metabolism
25	5,380,526 -	Antidiabetic Agent and Method of Treating Diabetes
	5,422,125 -	Method and Composition for Treatment of Insulin Resistance Syndromes
30	5,424,406 -	Dihydrochalcone Derivatives which are Hypoglycemic Agents
	5,444,086 -	Naphthalenylmethyl Thiophenones as Antihyperglycemic Agents
35	5,468,755 -	Therapeutic Process for the Treatment of the Pathologies of Type II Diabetes
40	5,478,852 -	Use of Thiazolidinedione Derivatives and Related Antihyperglycemic Agents in the Treatment of Impaired Glucose Tolerance in Order to Prevent or Delay the Onset of Noninsulin-Dependent Diabetes Mellitus
45	5,510,360 -	Azolidinediones as Antihyperglycemic Agents
50	5,532,256 -	New Azolidinediones and Thiadiazolidinediones as Antihyperglycemic Agents
55	5,589,183 -	Method and Apparatus for Treatment of Neurogenic Diabetes Mellitus, and Other Conditions

5,595,763 - Tungsten (VI) Compositions for the Oral
Treatment of Diabetes Mellitus

SUMMARY OF INVENTION

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The invention is directed to a method and composition for the treatment of diabetes mellitus including Type I, IGT and Type II diabetes mellitus. More specifically, this invention pertains to a novel method of
10 treating diabetes mellitus by incorporating a therapeutic amount of one or more insulin sensitizers along with one or more of an orally ingested insulin, an injected insulin, a sulfonylurea, a biguanide or an alpha-glucosidase inhibitor for the treatment of diabetes mellitus. A therapeutic
15 amount of insulin sensitizer can comprise one microgram to 10 grams of one or more insulin sensitizers combined or used with one or more of:

- 20 a. A therapeutically effective amount of an orally ingestible insulin which withstands degradation by passage through the stomach and upper intestine of the mammal so that a therapeutically effective level of insulin reaches the bloodstream of the mammal. The addition of the insulin sensitizer is to sensitize the
25 cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the orally ingested insulin required for a therapeutic dose, and/or,
- 30 b. An injected insulin product. The addition of the insulin sensitizer is to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the therapeutic dose required of injected
35 insulin, and/or,
- c. A sulfonylurea. The addition of the insulin sensitiz-

er is to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the required therapeutic dose of the sulfonylurea, and/or,

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d. A biguanide. The addition of the insulin sensitizer is to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the required therapeutic dose of the biguanide, and/or,

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e. A alpha-glucosidase inhibitor. The addition of the insulin sensitizer is to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the required therapeutic dose of the alpha-glucosidase inhibitor.

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The invention is directed to a method for the treatment of diabetes mellitus comprising administering to a person afflicted with diabetes mellitus a therapeutic amount of an insulin sensitizer with a therapeutic amount of a drug selected from the group consisting of: (a) an orally ingestible insulin; (b) an injectible insulin; (c) a sulfonylurea; (d) a biguanide; and (e) an alpha-glucosidase inhibitor.

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The invention is also directed to a composition for the treatment of diabetes mellitus comprising: (a) a therapeutic amount of an insulin sensitizer; and (b) a therapeutic amount of a drug selected from the group consisting of: an orally ingestible insulin; an injectible insulin; a sulfonylurea; a biguanide; and an alpha-glucosidase inhibitor.

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The method and composition can include adding a pharmaceutically acceptable carrier to the composition.

DETAILED DESCRIPTION OF SPECIFIC
EMBODIMENTS OF THE INVENTION

5 The addition of an insulin sensitizer to drugs
used for the treatment of diabetes mellitus reduces the
required dosage of these drugs due to the increased uptake
of glucose facilitated by the insulin sensitizer.

10 I have discovered unexpectedly that it is poss-
ible to overcome the problem of insufficient bloodstream
levels of insulin typically associated with orally ingested
insulin by incorporating an orally ingestible insulin
sensitizer with an orally ingestible insulin composition.
While I do not wish to be bound adversely by any
15 unsupported or invalid theories, the following description
is offered as a possible explanation of why the combination
of an orally ingestible insulin and an orally ingestible
insulin sensitizer overcomes the problem caused by less
than a therapeutic amount of insulin reaching the
20 bloodstream when insulin is administered orally to a
patient.

As discussed previously, in typical oral
ingestible insulin situations to date, insufficient levels
25 of insulin reach the bloodstream of the diabetic person
because most of the insulin is destroyed in the stomach and
gut of the diabetic person. However, as I have discovered,
if an orally ingestible insulin sensitizer is added to the
composition, and such sensitizers are not adversely
30 affected by the strong digestive processes of the stomach
and gut, the insulin sensitizer enables the lower levels of
insulin that reach the bloodstream to be sufficient for
purposes of enabling the cells of the body to function with
the lower levels of insulin. In other words, the insulin
35 sensitizer sensitizes the insulin insensitive cells of the
body of the diabetic so that even low levels of insulin are
able to attach to facilitate required glucose uptake by the

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cells. Hence there is sufficient glucose uptake by the cell to enable sufficient metabolism.

My discovery is also applicable to insulin
5 injection. When insulin is injected intravenously, in
combination with an insulin sensitizer, less insulin is
required to achieve the same therapeutic effect in the
body. The insulin sensitizer increases the utilization of
glucose at any given insulin level, so less insulin is
10 required for an equal therapeutic result.

My discovery has application to other diabetes
treatments, methods and drugs. When a sulfonylurea is used
to stimulate insulin production and control diabetes
15 mellitus, including an insulin sensitizer with the
sulfonylurea, less of the sulfonylurea is required to
achieve the same therapeutic effect in the body. As the
amount of insulin sensitizer increases the utilization of
glucose at any given insulin level, less insulin is
20 therefore required to be manufactured by the beta cells of
the pancreas for an equal therapeutic result and as a
result less of the sulfonylurea may be used. Adverse side
effects are reduced by lower levels of sulfonylurea.

25 When a biguanide is used to control diabetes
mellitus, the amount of the biguanide required can be
reduced and yet the same blood glucose levels in the body
can be achieved when an insulin sensitizer is included with
the biguanide. The insulin sensitizer increases the
30 utilization of glucose at any given insulin level. As a
biguanid reduces the amount of glucose delivered to the
blood, reducing the amount of the biguanid will increase
the glucose delivered to the blood which can be utilized by
the body due to the addition of the insulin sensitizer.
35 Also, adverse side effects are reduced.

My discovery can also be applied to alpha-

glucosidase inhibitors. When an alpha-glucosidase inhibitor is used to control diabetes mellitus, less of the alpha-glucosidase inhibitor is required to achieve the same blood glucose levels in the body when an insulin sensitizer is included. The insulin sensitizer increases the utilization of glucose at any given insulin level. Since an alpha-glucosidase inhibitor reduces the amount of glucose delivered to the blood, reducing the amount of the alpha-glucosidase inhibitor due to the addition of the insulin sensitizer will increase the level of glucose delivered to the blood which can be utilized by the body.

The subject compositions according to the invention can be administered parentally, topically or internally, but preferably orally, since that is the easiest form of administration. The compositions according to the invention may be formulated in any suitable orally acceptable form by employing conventional formulation techniques and conventional pharmaceutically acceptable formulation ingredients. The subject compositions according to the invention may, for example, be employed in nutritionally acceptable forms by incorporation of the compositions in a fibre supplement, a meal replacer, or a drink mix, or in pharmaceutically acceptable forms such as tablets or capsules in admixture with pharmaceutically acceptable carriers. The compositions according to the invention may also be used in combination with other pharmaceutically acceptable agents, for which the disclosed composition may be formulated in one unit with the other pharmaceutically effective agents, or in separate units administered at the same time or at separate times during a 24 hour period. The compositions according to the invention may be administered in single dosage form or in the form of sub-units several times a day.

Example

G.B. - Case History

5 G.B. is a Type I diabetic who must normally
inject insulin intravenously twice a day in order to
control her Type I condition. At the suggestion of the
inventor, G.B. volunteered one day to determine whether or
not the addition of a small amount of an insulin sensitizer
to her insulin injection would enable a lower level of
10 insulin to be administered intravenously. At 8:30 a.m.,
G.B. injected intravenously her usual insulin dosage and at
the same time ingested 120 mg of an oral insulin sensitizer
known as V-411 (sold under the trade-mark DIAB II by
Biotech Holdings Ltd.). By 11:00 a.m., the same morning,
15 G.B. went into a hypoglycaemic state involving rapid heart
beat, trembling, dizziness and other symptoms normally
associated with hypoglycaemia, a condition which G.B. was
familiar with. G.B. immediately started sucking sugar
cubes to endeavour to raise the sugar level in her blood
20 and alleviate the hypoglycemic condition. However, it
still took about an hour for her to stabilize her
hypoglycaemic condition. The proper treatment might have
been for G.B. to immediately go the emergency ward of a
hospital for a glucose injection.

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It was clear from G.B.'s experience with the
addition of the V-411 insulin sensitizer that the effects
of the insulin sensitizer were very pronounced and a normal
dosage of G.B.'s normal insulin injection resulted in a
30 condition whereby the glucose in her blood was being
utilized by the cells of her body at such a high rate of
efficiency that she experienced a hypoglycaemic condition.
It appeared clear that there was a startling effect, and
indeed perhaps a synergistic effect, created between the
35 combination of insulin and the V-411 insulin sensitizer.
Thus, much smaller dosages of insulin could have been used.
Indeed, it was hypothesized that such dosages could be of

the same low level as experienced with orally administered insulin.

5 V-411 insulin sensitizer is known by the inventor
to withstand the degradation effects of the gastric juices
of the stomach and enzymatic action of the gut. Because of
the strong or synergistic effect involving the combination
of insulin and the insulin sensitizer, it follows that the
10 inclusion of an insulin sensitizer in combination with an
orally ingestible insulin should enable the orally
ingestible insulin to work effectively in the treatment of
diabetes mellitus. This is because the levels of insulin
that must ultimately reach the bloodstream are greatly
reduced, and such low levels are sufficient due to the
15 effects of the insulin sensitizer.

As will be apparent to those skilled in the art
in the light of the foregoing disclosure, many alterations
and modifications are possible in the practice of this
20 invention without departing from the spirit or scope
thereof. Accordingly, the scope of the invention is to be
construed in accordance with the substance defined by the
following claims.

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